ISCT CGTP Workshop 2005
"Overview of CGTP Requirements"

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Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement. Final Rule

Published Nov. 24, 2004

(69 FR 68612)

Effective May 25, 2005

21 CFR Part 1271, subparts D, E, F

Subpart D--Current Good Tissue Practice [1271.145-150]

- Recover, process, store, label, package, and distribute HCT/Ps, and screen/test donors (CGTP includes subpart C), to prevent introduction, transmission, and spread of communicable disease
- Ensure that HCT/Ps do not contain communicable disease agents, are not contaminated, and do not become contaminated during manufacturing
- Communicable disease agents include viruses, bacteria, fungi, parasites, and TSE agents

CGTP—General [1271.150(a)]

- Methods used in, and facilities and controls used for manufacture of HCT/Ps
- CGTPs focus on prevention of communicable disease transmission
- Broad goals applicable to the wide range of HCT/Ps
- Establishments have the flexibility to determine how to meet goals through their SOPs

Core CGTP Requirements [1271.150(b)]

- Requirements most directly related to preventing the introduction, transmission, or spread of communicable disease agents and disease (e.g., facility sanitation; storage at appropriate temp.)
- Other requirements support the core CGTP requirements (e.g., procedures for core CGTP requirements; quality program designed to ensure compliance with core CGTP requirements;

Core GTPs (10)

- **Facilities** [1271.190(a) and (b)]
- **Environmental control** [1271.195(a)]
- **Equipment** [1271.200(a)]
- **Supplies and reagents** [1271.210(a) and (b)]
- **Recovery** [1271.215]
- **Processing and process controls** [1271.220]
- **Labeling controls** [1271.250(a) and (b)]
- **Storage** [1271.260(a)–(d)]
- **Receipt, pre-distribution shipment, distribution** [1271.265(a)-(d)]
- **Donor eligibility determination (donor screening and donor testing)** [1271.50, 1271.75, 1271.80, 1271.85]

Compliance with applicable requirements—Manufacturing Arrangements [1271.150(c)(1)]

- Comply with the requirements applicable to the operations you perform
- If you have a contract with another establishment to perform some manufacturing steps for you—
  - Before entering the contract, ensure that the other establishment complies with applicable CGTPs for the steps it performs
  - If you become aware that establishment may no longer be in compliance, take reasonable steps to ensure that the other establishment complies
  - If you determine that establishment is not in compliance, terminate the contract

Available for Distribution [1271.150(c)(2)]

- The establishment that determines that an HCT/P meets all release criteria and makes the HCT/P available for distribution is responsible for reviewing manufacturing and tracking records to determine that the HCT/P has been manufactured in compliance with subparts C and D

Compliance with 210, 211, 820 [1271.150(d)]

- Conforming amendments to these parts require HCT/Ps that are also regulated as biological drugs or medical devices to follow 1271 subparts C and D
- Requirements supplement but do not supersede each other
- In the event of a conflict with a requirement in part 1271 and in parts 210, 211, or 820, the regulations more specifically applicable to the product in question (i.e., the drug or device) supersede the more general

"Where appropriate" [1271.150(e)]

- The requirement is appropriate unless you can document justification otherwise.
- A requirement is appropriate if non-implementation of the requirement could reasonably be expected to result in the HCT/P not meeting its specified requirements, or in your inability to carry out any necessary corrective action.

Requirements
(* indicates Core CGTPs)

- Exemptions and Alternatives
- Quality Program
- Personnel
- Procedures
- Facilities*
- Environmental Control and Monitoring*
- Equipment*
- Supplies/Reagents*
- Recovery*

Requirements, cont. (* indicates Core CGTPs)

- Processing and Process Controls*
- Process Changes
- Process Validation
- Labeling Controls*
- Storage*
- Receipt, Pre-Distribution Shipment, Distribution*
- Records
- Tracking
- Complaint File

Exemptions and Alternatives [1271.155]

- Written (or oral under certain circumstances) request to any requirement in subpart C or D
- Submit to Director of Center
- Director may grant if submitted information justifies an exemption or proposed alternative satisfies the purpose of requirement, and consistent with goals of protecting public health
- Wait until granted by FDA to begin
- Document start date
- Center director may issue an exemption or alternative in a public health emergency

Quality Program [1271.160 (a),(b)]

- All HCT/P establishments must have a QP
- Establish/maintain procedures relating to core CGTP requirements; review, approve, revise
- Ensure that procedures exist for receiving/evaluating/sharing information relating to core CGTP requirements with other establishments that are known to have recovered HCT/Ps from the same donor, and with other establishments that are known to perform any manufacturing step
- Notify consignees, do recalls and reporting as necessary

Quality Program, cont.

- Ensure that corrective action is taken—short and long-term action to prevent recurrence
- Ensure proper training/education of personnel involved in core CGTP activities
- Establish/maintain monitoring systems
- Investigate/document/trend HCT/P deviations relating to core CGTP requirements

Audits [1271.160(c)]

- Periodically perform audits of activities related to core CGTP requirements for management review
- “Quality audit”—a documented, independent inspection and review of an establishment’s activities related to core CGTP requirements, to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review

Computers [1271.160(d)]

- Validate computer software for its intended use if you rely on software to comply with core CGTPs and if the software is custom software, or commercially available software customized or programmed for you (e.g., software programmed to perform a user-defined calculation, table)
- All other software—verify for its intended use if used for a core CGTP requirement

Personnel [1271.170]

- Sufficient number to comply with requirements
- Have necessary education, experience, and training to ensure competent performance of assigned functions
- Must perform only those functions for which qualified and authorized
- Train and retrain as necessary

Procedures [1271.180]

- Establish and maintain procedures appropriate to meet core CGTP requirements
- Review and approve before implementing
- Readily available to personnel in the area where these functions are performed, or nearby area
- Can adopt current standards from another organization, if you verify that they meet the requirements of this part and are appropriate for operations performed

Facilities [1271.190]

- Suitable size, location, construction; maintained in a good state of repair
- Clean/sanitize/order the facility to prevent transmission of communicable disease through contamination or cross-contamination
- Maintain separate areas for each operation, or have other control systems to prevent improper labeling, mix-ups, cross-contamination
- Have procedures (including cleaning methods and schedules)
- Keep records of all cleaning/sanitation for 3 yrs.

Environmental Control and Monitoring [1271.195]

- Where conditions could reasonably be expected to cause contamination/cross-contamination of HCT/Ps or equipment, or exposure to communicable disease agents:
- Control environmental conditions (temperature, humidity, ventilation, air filtration, cleaning and disinfecting rooms, maintenance of equipment used to control conditions necessary for aseptic processing, where appropriate); document
- Monitor environmental conditions, including microorganisms where appropriate; document

Equipment [1271.200]

- Suitably located and installed
- Clean, maintain, inspect routinely
- Where appropriate, routinely calibrate all automated, mechanical, electronic equipment used for inspection, measuring and testing
- Establish and maintain procedures
- Keep records of maintenance, cleaning, calibration on or near equipment; make records available to staff using the equipment
- Relate each HCT/P to equipment used in manufacturing

Supplies and Reagents [1271.210]

- Do not use until you verify that they meet specifications designed to prevent circumstances that increase the risk of communicable disease—vendor or user verification
- Validate and/or verify reagents made in-house
- Use sterile reagents when processing or preserving the HCT/P, where appropriate
- Keep records of receipt and verification
- Relate the lot of the supply or reagent used in manufacturing to HCT/P

Recovery [1271.215]

- Recover HCT/Ps in a way that does not cause contamination or cross-contamination during recovery or otherwise increase risk of communicable disease transmission through use of the HCT/P
- Very broad requirement, with recommended methods in guidance

Processing and Process Controls [1271.220]

- Process in a way that does not cause contamination or cross-contamination during processing and that prevents communicable disease transmission
- Human cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacture
- Ensure that specified requirements for in-process control are met; that each HCT/P is controlled until required inspection and testing are completed and approved
- Sampling of in-process HCT/P must be representative of the material to be evaluated

Process Changes [1271.225]

- Verify or validate each change to a process to ensure that the change does not create an adverse impact elsewhere in the operation
- Approve before implementation
- Communicate change to appropriate personnel in a timely manner

Process Validation [1271.230]

- When the results of processing cannot be fully verified by subsequent inspection and tests, you must validate and approve a process according to established procedures; document
- Any written representation that your processing methods reduce the risk of communicable disease transmission (e.g., sterility, pathogen inactivation) must be based upon a fully verified or validated process
- A change to a validated process must be reviewed and evaluated, and re-validated where appropriate

Labeling Controls [1271.250]

- Establish/maintain procedures to control labeling so as to ensure proper identification and to prevent mix-ups
- Verify label accuracy, legibility, and integrity
- Ensure that HCT/P is labeled in accordance with (1) all labeling requirements in the DE rule, and that each HCT/P is accompanied by documentation of the donor eligibility determination; (2) tracking requirements

Storage [1271.260]

- Control storage areas to prevent mix-ups, contamination, cross-contamination of HCT/Ps, supplies and reagents
- Prevent an HCT/P from being improperly made available for distribution
- Appropriate temperature—establish temperature limits for storage at each step of manufacturing; maintain, record and review storage temperatures
- Expiration date, where appropriate, based on type of HCT/P, processing, preservation, storage conditions and packaging

Receipt, Pre-Distribution Shipment, Distribution [1271.265]

- Evaluate each incoming HCT/P for presence and significance of microorganisms, and inspect for damage and contamination
- Accept, reject, or place in quarantine based on pre-established criteria
- Pre-distribution shipment before HCT/P is available for distribution—pre-established criteria met; ship in quarantine
- Before making the HCT/P available for distribution—review manufacturing and tracking records and verify that release criteria have been met; documentation by responsible person

Cont.

- Packaging and shipping containers designed and constructed to prevent HCT/P contamination and to maintain appropriate shipping conditions
- Establish appropriate shipping conditions during transit
- Document—identify the HCT/P and establishment that supplied it; activities performed, dates and results; quantity; disposition (e.g., identify of consignee)

Records [1271.270]

- Maintain records concurrently with the performance of each step
- Records must be accurate, indelible, legible
- Records must identify the person performing the work, dates, provide a complete history of the work performed
- Have a records management system relating to core CGTP requirements—records of each HCT/P's history and manufacture, including labeling and packaging procedures, equipment logs

Cont.

- Maintain original paper records or copies; records maintained electronically must be backed up
- Retain records for 10 years after date of administration of HCT/P, or if date of administration is not known, 10 years after date of distribution, disposition, or expiration, whichever is latest (except for cleaning/sanitation records—3 year retention)
- Keep records of contracts and agreements with other establishments—name, responsibilities

Tracking [1271.290]

- If you perform any step in manufacture in which you handle the HCT/P, track it to facilitate investigation of actual or suspected communicable disease transmission
- Have a system that enables tracking of all HCT/Ps from donor to consignee or final disposition, vice versa; may participate in another establishments tracing system; list of consignees; record the disposition of each HCT/P
- Inform consignee in writing of these tracking requirements and of your tracking system

Cont.

- Each HCT/P must have a distinct identification code that relates HCT/P to donor and all records
- Labeling accompanying the distributed HCT/P that includes information designed to facilitate effective tracking, using the distinct identification code, from the donor to the recipient, vice versa (e.g., card to return to bank indicating disposition)
- Distinct id code must not include an individual's name, SS#, or medical record# (except for autologous or directed donations*)
- You may use the code assigned by another establishment, but if you assign a new code, relate it to the old one

Complaint Files [1271.320]

- Establish/maintain a record of complaints related to core CGTP requirements in a file available for FDA review
- As soon as practical, review, evaluate, and investigate a complaint related to core CGTPs to determine if it is a deviation or adverse reaction, and if it needs to be reported to FDA
- If not reportable, determine whether an investigation is necessary or not (document reason)
- Determine whether this is an isolated event or represents a trend

Subpart E—Additional Requirements for non-reproductive "361" HCT/Ps [1271.350]

- Reporting Adverse Reactions to FDA--Investigate any adverse reaction involving a communicable disease related to an HCT/P that you made available for distribution
  - Adverse reaction is a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response
  - Report to FDA (Form FDA 3500A) within 15 days (and F/U report) if fatal, life-threatening, results in permanent impairment of a body function or permanent damage to a body structure, OR necessitates medical or surgical intervention, including hospitalization

1271.350 cont.

- Reporting HCT/P Deviations to FDA--Investigate all deviations related to a distributed HCT/P for which you performed a manufacturing step
  - A deviation from regulations, standards, specifications, or an unexpected event that relate to the prevention of communicable disease transmission or HCT/P contamination
  - Report deviations relating to core CGTPs if they occur in your facility or a facility under contract with you, within 45 days of occurrence
  - Include information on follow-up actions
  - **[Note: Requirements for reporting adverse events and biological product deviations for licensed "351" HCT/Ps are contained in 600.80 and 600.14]**

Subpart E—Additional Requirements for non-reproductive "361" HCT/Ps [1271.370]

- HCT/P label
  - Distinct identification code affixed to container label
  - Type of HCT/P
  - Expiration date, if any
  - Warnings, if required in DE rule and if applicable
- HCT/P label or accompanying HCT/P
  - Name and address of establishment that made HCT/P available for distribution
  - Storage temperature
  - Instructions for use when related to communicable disease transmission

Questions

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